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Variability of formulas to assess insulin sensitivity and their association with the Matsuda index

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Abstract

Objective: **To assess the individual variability of HOMA and QUICKI indexes for the assessment of insulin resistance, using three fasting blood samples obtained within 30 minutes.**

Research methods & procedures: **Data from 80 participants aged 41.5 ± 15 years (26 females), who underwent an oral glucose tolerance test to calculate Matsuda index, were used. Every participant had three fasting blood samples obtained within 30 minutes and four blood samples obtained at 30, 60, 90 and 120 minutes after a 75 g oral glucose load. Insulin and glucose were measured in each sample. HOMA and QUICKI indexes were calculated using the nine possible combinations of the three fasting blood samples. Matsuda index was calculated with all samples obtained.**

Results: **Median values of HOMA-IR, HOMA-β, QUICKI and Matsuda indexes were 1.9, 117.9, 0.35 and 3.71 arbitrary units, respectively. The individual variation coefficients of HOMA-IR, HOMA-β and QUICKI were 11.8 (7.8-18.9), 15 (10.2-22.9) and 1.8 (8.8-21.9) % respectively. When compared with Matsuda index, the R squared values of HOMA-IR, HOMA-β and QUICKI were 0.46, 0.2 and 0.71, respectively.**

Conclusions: **Among fasting indexes for insulin resistance, QUICKI had the lower variation coefficient and the higher correlation with Matsuda index.**

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Key words: *HOMA. Matsuda. QUICKI.*

VARIABILIDAD DE LAS FÓRMULAS QUE EVALÚAN LA SENSIBILIDAD A LA INSULINA Y SU ASOCIACIÓN CON EL ÍNDICE MATSUDA

Resumen

Objetivo: **Evaluar la variabilidad individual de los índices HOMA y QUICKI para resistencia a insulina, utilizando tres muestras de sangre en ayunas obtenidas en un período de 30 minutos.**

Material y métodos: **Se utilizaron datos provenientes de 80 participantes de 41.5 ± 15 años de edad (26 mujeres) a quienes se les efectuó una prueba de tolerancia a glucosa oral para calcular el índice de Matsuda. A cada participante se le tomaron tres muestras de sangre en ayunas en un período de 30 minutos y cuatro muestras a los 30, 60, 90 y 120 minutos después de una carga oral de 75 g de glucosa. En cada muestra se midieron los niveles de insulina y glucosa. Los índices HOMA y QUICKI se calcularon utilizando las nueve combinaciones posibles con las tres muestras obtenidas en ayunas. El índice de Matsuda se calculó utilizando todas las muestras.**

Resultados: **Las medianas de los índices HOMA-IR, HOMA-β, QUICKI y Matsuda fueron 1,9, 117,9, 0,35 and 3,71 unidades arbitrarias, respectivamente. Los coeficientes de variación individual del HOMA-IR, HOMA-β y QUICKI fueron 11,8 (7,8-18,9), 15 (10,2-22,9) and 1,8 (8,8-21,9) %, respectivamente. Comparados con el índice de Matsuda, los valores de R^2 para el HOMA-IR, HOMA-β y QUICKI fueron 0,46, 0,2 y 0,71, respectivamente.**

Conclusiones: **De los índices que utilizan muestras en ayunas para determinar resistencia a insulina, el QUICKI es el que tiene el menor coeficiente de variación y la mejor correlación con el índice de Matsuda.**

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Palabras clave: *HOMA. Matsuda. QUICKI.*

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Introduction

Insulin resistance (IR) is defined as a lower biological effect of insulin on target tissues. IR constitutes the main defect underlying the pathogenesis of type 2 diabetes mellitus and is also associated with obesity and metabolic syndrome.[1,2]

The best method to assess insulin sensitivity is the euglycemic hyperinsulinemic clamp, which is considered the gold standard for comparison with other methods. However, it is a complex test that is mainly reserved for research purposes and rarely performed in clinical settings.[3] In 1985, Mathew et al. devised and index to assess insulin sensitivity, based on three fasting insulin and glucose measurements. It is called the homeostasis model assessment (HOMA-IR),which shows a good correlation with the euglycemic clamp[4] and is a good predictor for the future appearance of clinical diabetes mellitus.[5,6] However, its individual variability may be as high as 30%, due to pulsatile secretion of insulin and the influence of stress or exercise.[4] Its cutoff point changes in different populations.[7,8] There is also a complementary formula that calculates beta cell function, called HOMA-β.[4]

Previous studies performed in Chile using HOMA-IR in Young adults and older people have reported cutoff points for insulin resistance of 2.5 and 2.6, respectively. Unfortunately, in both studies, HOMA-IR was calculated using only one fasting blood sample. Therefore no information about the variability of the method can be gathered from these studies.[9,10]

The high variability of HOMA-IR, motivated the proposal of a new formula to calculate insulin sensitivity that relies less on insulin levels, which is called quantitative insulin sensitivity check index (QUICKI).[11]

Some authors have observed that QUICKI has a better correlation with the euglycemic clamp than HOMA-IR and a lower coefficient of variation. Sarafidis et al and Antuna et al reported a coefficient of variation for this index, based on two fasting glucose and insulin samples, of 7.8 and 3.9% respectively.[12,13] Even considering these advantages, the formula is rarely used in clinical studies.

In 1999, Matsuda and De Fronzo proposed a new method to assess insulin sensitivity, that required serial determinations of glucose and insulin before and after a glucose load and that had a good correlation with the results of euglycemic hyperinsulinemic clamp (r = 73). This method is known as the Matsuda De Fronzo index. Compared to the euglycemic clamp, it is simpler to perform and has a good correlation with the euglycemic clamp. It can be reasonably used as a standard to compare with the other methodologies to estimate insulin resistance.[3,14]

We have performed glucose and insulin curves to calculate the Matsuda index in several clinical studies involving healthy participants. Since this index requires obtaining three fasting blood samples to measure glucose and insulin, we were able to calculate the individual variability of HOMA-IR and QUICKI in nine different combinations of samples (three blood glucose and three insulin levels), obtained within 30 minutes in the same individual. Thus, the aim of this study is to report the variability of these formulas that depend on fasting sampling, to assess insulin sensitivity and their association with the results of the Matsuda index.

Material and methods

We analyzed data from 80 healthy participants aged 22 to 78 years (26 women), with a body mass index ranging from 20.3 to 33.8 kg/m^2, who participated in two clinical research cross sectional protocols. Subjects with fasting hyperglycemia, cancer, renal liver or heart failure were excluded from the study. All subjects signed an informed consent to participate in the clinical research studies and specifically allowing researchers to perform secondary analyses with the gathered clinical and laboratory data.

All participants were interrogated about history of previous diseases and their weight, height, waist and hip circumference were measured. After a 12 hours fast, a venous line was placed in an antecubital vein. Three fasting blood samples were drawn every 15 minutes for 30 minutes. Posteriorly they ingested a 75 g glucose load and further blood samples were drawn at 30, 60, 90 and 120 min, after the ingestion of the glucose load. Blood lipids and TSH levels were also measured in the first fasting blood sample obtained, and glucose and insulin were measured in all blood samples obtained. All laboratory determinations were carried out at Laboratorio Vida Integra, using routine laboratory techniques. Insulin was measured by chemoluminiscence using a Roche Modular equipment.

Using fasting and post glucose load blood samples, the Matsuda index was calculated according to the formula:

$$\frac{10{,}000}{\sqrt{(FPI^{*}\,FPG)\,*\,(xGPC^{*}\,xIPC)}}$$

Where FPI is fasting plasma insulin expressed as uU/ml, FPG is fasting plasma glucose expressed as mg/dL, xGPC is mean plasma glucose concentration after the load and xIPC is the mean insulin concentration after the load.

With fasting glucose and insulin levels, the following insulin sensitivity parameters were calculated:

1. HOMA-IR = (Fasting insulin (uU/ml)* Fasting blood glucose (nmol/l))/22.5.
2. HOMA- = (20 * fasting insulin (uU/ml))/(Fasting blood glucose (mmol/L)-3.5).
3. QUICKI = 1/[log fasting plasma insulin (uU/ml) + log fasting blood glucose(mg/dl)].

Table I
Demographic, anthropometric and laboratory features of participants, expressed as median (p25-p75)

	Females (n = 26)	*Males (n = 54)*	*p¶*
Demographic and anthropometric data			
Age (years)	32 (28-37)	46.5 (41-70)	< 0.01
Body mass index (kg/m^2)	27.4 (26.1-28.5)	25.5 (23-27.8)	< 0.01
Waist circumference (cm)	94.8 (91-98.5)	92.8 (88-99)	NS
Hip circumference (cm)	102.3 (101-105.5)	96.8 (94.5-100)	< 0.01
Blood lipids and thyroid stimulating hormone			
Total cholesterol (mg/dL)	178.5 (163-214)	194 (162-221)	NS
HDL cholesterol (mg/dL)	48 (41-63)	44.5 (38-55)	NS
Triacylglycerol (mg/dL)	97.5 (67-117)	132 (93-162)	0.03
Thyroid stimulating hormone (μU/ml)	2.1 (1.5-2.9)	2.4 (1.4-3.7)	NS
Parameters of insulinsensitivity			
Fasting glucose (mg/dL)§	87 (79-93)	91.5 (86-97)	< 0.01
Fasting insulin (μU/ml)§	11.4 (9.7-14.2)	7.7 (5.6-10.5)	< 0.01
Matsuda index	3.4 (2.6-4.6)	4.2 (3-5.5)	0.04
HOMA-IR§	2.3 (1.8-3)	1.6 (1.2-2.3)	< 0.01
HOMA-β§	183.4 (129-263.1)	92.8 (73.5-126.2)	< 0.01
QUICKI§	0.3 (0.3-0.4)	0.4 (0.3-0.4)	< 0.01

§Using the mean of three fasting values.
¶Probability for gender differences (Kruskal Wallis).

As there were three fasting samples available for glucose and insulin measurement for each subject, nine possible combinations of values were used to calculate the above mentioned parameters.

Statistical analysis

The normality of variable distribution was determined using the Shapiro Wilk test. Variables with a normal distribution are expressed as mean ± standard deviation. Variables with a non-normal distribution are expressed as median (p25-p75). The significance of differences between median values was calculated using the Kruskal Wallis test. Using the nine possible calculations, the individual variation coefficients for fasting glucose, insulin and insulin sensitivity parameters were calculated as (standard deviation of the parameter/mean)*100. The Matsuda index was used as the gold standard to determine insulin sensitivity. Linear regression equations were used to calculate the association between the Matsuda index and the fasting parameters of insulin resistance, using the mean of all nine calculations performed for HOMA and QUICKI. Since all these parameters had different units of measure, no effort was made to carry out concordance analyses.

Results

The anthropometric and laboratory features of participants are depicted in table I. Compared to men, women were younger, had a higher body mass index and hip circumference. Women also had higher fasting insulin levels, HOMA-IR, HOMA-β and lower glucose and triacylglycerol levels, Matsuda and QUICKI indexes. The coefficients of variation of HOMA-IR, HOMA-β and QUICKI, fasting insulin and glucose measured on the same day and in the same individual within 30 min are shown in table II. For HOMA-IR and HOMA-β, coefficients of variation were more than 10%. Among the three indexes, QUICKI had the lower coefficient of variation (< 3%), similar to the variability of fasting glucose. QUICKI and fasting insulin had less variation

Table II
Variation coeficients of measured parameters of insulin sensitivity, expressed as median (p25-p75)

	Females	*Males*	*Total Sample*	*p¶*
HOMA-IR	9.3 (7.8-12.8)	14.5 (7.5-21.9)	11.8 (7.8-18.9)	NS
HOMA-β	12.9 (9.9-15.9)	16.5 (11.1-23.3)	15 (10.2-22.9)	NS
QUICKI	1.4 (1.2-1.9)	2.1 (1.1-3.3)	1.8 (1.1-2.9)	0.05
Fasting insulin	10.6 (9-14.8)	16.4 (8.2-24)	13.4 (8.8-21.9)	0.05
Fasting glucose	1.5 (1.2-2.6)	2.3 (1.6-3.4)	2.2 (1.3-3.4)	NS

¶Probability for gender differences (Kruskal Wallis).

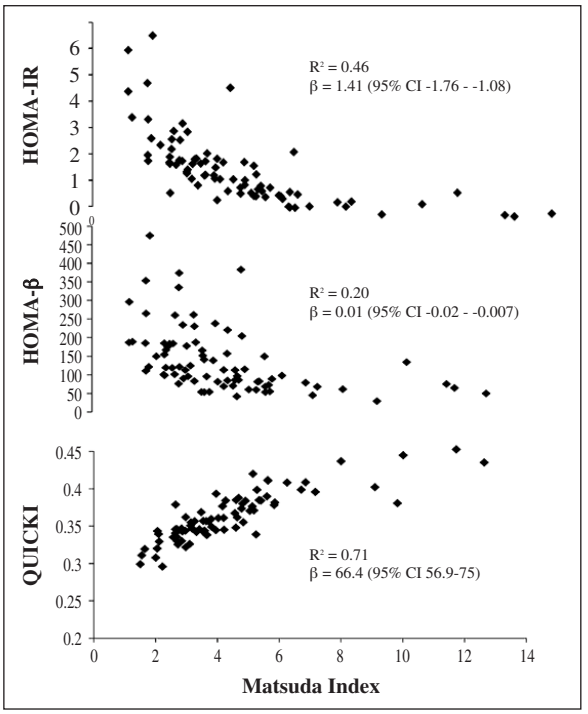

Fig. 1.—Regression plots for the association between Matsuda index and HOMA-IR, HOMA-β and QUICKI indexes. R^2 corresponds to the squared correlation coefficient; β corresponds to the estimated coefficient of the independent variable.

in women than in men. No differences by gender were observed for HOMA-IR, HOMA-β and fasting glucose. No associations between coefficients of variation and other demographic or biologic features of participants were observed. The regression plots between MATSUDA index and fasting parameters are shown in figure 1. The best R^2 was observed for QUICKI ($R^2 = 0.71$) and the worst for HOMA-β ($R^2 = 0.20$).

Discussion

We found that, as reported previously, HOMA has a high individual variability, when calculated using only one fasting and insulin value. QUICKI had the lowest coefficient of variation and the best correlation with Matsuda.

HOMA-IR is frequently used to assess insulin sensitivity and clinical decision making, such as indication of pharmacological treatments. It is also used to evaluate therapeutic results. Therefore, clinicians should be aware that these decisions are based on a highly variable parameter, which can change as much as 12% within 30 minutes if it is based solely on one blood sample. Even large epidemiological studies that have defined cutoff points for insulin resistance, have not taken into account this weakness of the index and are based on only one fasting sample per participant.[15,16]

Surprisingly, QUCKI index is rarely used for the same purposes, probably because it is less known and requires log transformation. Considering these results, this formula should be the best choice to determine insulin resistance. However, the enthusiasm with this index must be toned down since a study performed in critical patients found no association between M values derived from clamp and QUICKI.[17] However critical patients behave differently in several metabolic aspects.

The comparison of HOMAIR with clamp results was originally tested by the authors who described the method. In 12 normal individuals and 11 diabetic patients, they found correlation coefficients with M values of -0.83 and -0.92 respectively.[4] In another study performed in Korea in 47 diabetic patients, 21 subjects with glucose intolerance and 22 normal individuals, the correlation coefficients of HOMA-IR with M values were -0.57, -0.41 and -0.40, respectively. The last two figures were not significant.[18]

We measured a variation coefficient for HOMA-IR that was lower than that reported by Antuna-Puente[13] and Sarafidis.[12] This difference may be explained by the fact that intrinsic variability of HOMA-IR is higher in diabetic patients than in normal subjects, as reported previously[19,20] and none of our participants was diabetic. The coefficient of variation of HOMA-IR is very similar to that of fasting insulin. This explains the advantage in terms of variability of QUICKI, which uses a logarithmic formula that relies less in fasting insulin than HOMA-IR. We do not have a plausible explanation for the higher variability of HOMA-IR, QUICKI and fasting insulin among men compared to women. However the women we studied were younger and had a higher body mass index. Therefore they were not entirely comparable with their male counterparts.

Putting these results in perspective, a warning must be generated concerning the use of insulin resistance indexes based on one single measurement of fasting insulin and glucose, when dealing with individual patients. Since there is a considerable variability in these parameters, clinical decisions, especially the use of pharmacological agents, should be very cautious. This is also valid when using these parameters to evaluate results of treatments. In the epidemiological setting, the variability is probably diluted by large sample of measurements. However the definition of cutoff values should be made using the three fasting samples proposed originally by Mathews et al.[4]

The main weakness of this work is that we used data coming from different studies. Therefore participants differ in age and body mass index. However the glucose load studies were performed by the same professionals using identical protocols and samples were processed in the same clinical laboratory. Therefore the results about individual variation are still reliable. Other weakness is the lack of a true gold standard such as euglycemic hyperglycemic clamp to perform the regression analysis. However Matsuda index is a reliable indicator for insulin resistance.[14] The main strength of the study is having and adequate number of participants that were studied by the same professionals and using exactly the same sampling protocol.

Conclusion

This study demonstrated that HOMA is a weak tool for diagnosis of insulin resistance due to its high within variability. On the contrary, QUICKI demonstrated a lower variation coefficient and a better correlation with Matsuda index and should deserve further assessments as a simple tool to assess insulin sensitivity.

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Conflicts of interest

The authors declare that they do not have any financial relationship with the organization that sponsored the research. Likewise they declare no conflicts of interest regarding the content of the manuscript.

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